and 56 can be found in original claims 13 and 14. Accordingly, these new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant appreciates Examiner Baker's time and consideration in the interview with Applicant's representative conducted on April 2, 2003. During the interview, it was brought to Examiner Baker's attention that the Radzicka et al. reference previously provided on an Information Disclosure Statement inadvertently omitted Table 1, pages 304-312. Applicant submits herewith a new Form 1449 with the complete citation and a complete copy of the reference.

Regarding the Restriction of New Claims

The restriction of claims 38-40 is respectfully traversed. The specification teaches that a common ligand refers to a ligand that binds to a conserved site in a receptor family (page 8, lines 29-31). The specification also teaches that a conserved site of an enzyme is a site that binds a cofactor (page 13, line 32, to page 14, line 2). The specification additionally teaches that a common ligand that binds to a conserved site can be determined by competition with a cofactor (natural common ligand)(page 13, line 32, to page 14, line 2; page 32, lines 26-30). Furthermore, the specification teaches that competing for cofactor binding is in fact a method for identifying a common ligand (page 32, lines 26-32). The specification thus clearly teaches that a common ligand binds to a conserved site and can be identified by competing for cofactor binding. Applicant

maintains that the examination of a claim reciting that the "common ligand competes for cofactor binding" is not an undue burden on the Examiner since the search of a claim reciting such a phrase would necessarily be encompassed by a search of a claim reciting a "common ligand to a conserved site in an enzyme family." Nevertheless, claims 38-40 have been canceled.

Rejections Under 35 U.S.C. § 103

The rejection of claims 9, 11-14, 37 and 41-43 under 35 U.S.C. § 103 as allegedly obvious over He et al., Bioorg. Med. Chem. Lett. 4:2845-2850 (1994), in view of Traxler et al., J. Med. Chem. 34:2328-2337 (1991), is respectfully traversed. Applicant maintains that the claimed methods are unobvious over He et al. in view of Traxler et al.

Applicant maintains, for the reasons of record, that claims 9, 11-14, 37 and 41-43 are unobvious over He et al., alone or in combination with Traxler et al. Nevertheless, to further prosecution, these claims have been canceled. Accordingly, this rejection has been rendered moot with respect to these claims and it is respectfully requested that this rejection be withdrawn.

Regarding new claims 44-56, Applicant submits that these claims are unobvious over He et al., alone or in combination with Traxler et al. With regard to He et al., this reference describes using a series of monoindolylmaleimides with different amine chains on the maleimide ring (page 2846; compounds 5-10 in Table 1, page 2848). The functions were

introduced in order to interact with the previously described acidic region (3 Asp in PKC of Figure 1) and to allow extension with a peptide sequence (page 2846; compounds 11-13, 15 and 16 in Table 1, page 2848). Compounds 5-10 and 14 (without amino acids) appear to have the closest analogy with a common ligand; for example, compound 6 is indicated to compete for ATP (page 2849). Compounds 5-10 and 14 also contain the amine chains "to interact with" the acidic region of PKC. Therefore, the compounds of He et al. analogous to common ligands are designed to interact with PKC, which is reflected in the specificity of these compounds shown in Table 1. Based on the teachings in He et al., there would have been no motivation to obtain compounds having specificity for any kinase other than PKC, let alone a dehydrognase or enzyme that binds the cofactor nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP), as claimed. Furthermore, there would have been no reasonable expectation of success that using the methods of He et al., in which the compound analogous to the common ligand is biased to interact with PKC, would provide a common ligand for any other kinase, let alone a bi-ligand to another kinase, or a common ligand or bi-ligand to a dehydrogenase.

He et al. describes using a PKC biased compound and adding amino acids allowing "the extension with peptidic sequence according to the bisubstrate concept" (page 2846, first complete paragraph). There is no suggestion or motivation to modify He et al. to identify bi-ligands for other enzymes because doing so would result in molecules that would not inhibit PKC, which is

contrary to the intended purpose of the reference, the design of PKC specific inhibitors.

Regarding Traxler et al., this reference does not teach or suggest a method of identifying a population of bi-ligands using a common ligand module. None of the compounds of Traxler et al. share a common ligand module. The sulfobenzoyl moiety is a diphosphate (ATP) mimic (see abstract). The nitrostyrene moiety is a tyrosine mimic. The compounds that contain the sulfobenzoyl moiety (compounds 5-23, Table II, page 2330) each differ in the sulfobenzoyl moiety, that is, none of the compounds are based on a common ligand module.

Even if Traxler provided motivation to search for bisubstrate inhibitors of other enzymes, as asserted in the Office Action, there would be no expectation that the combination of He et al., which describes a common ligand module biased towards PKC, with additional second ligands such as the tyrosine mimic nitrostyrene groups of Traxler et al., would provide the claimed method with a reasonable expectation of success.

The rejection of claims 9, 11-14, 37 and 41-43 under 35 U.S.C. § 103 as allegedly obvious over He et al., *supra*, in view of Traxler et al., *supra*, Rossman et al., The Enzymes, Volume XI, Part A, 3rd ed., P. Boyer, ed., Academic Press, New York (1975), and Radzicka et al., Methods Enzymol. 249:284-303 (1995), is respectfully traversed. Applicant maintains that the claimed methods are unobvious over He et al. in view of Traxler et al., Rossman et al. and/or Radzicka et al.

As discussed above, He et al., alone or in combination with Traxler et al., does not teach or suggest the claimed methods for identifying a population of bi-ligands to dehydrogenases in a dehydrogenase enzyme family. In particular, there would be no expectation that using the methods of He et al., which at best may be considered to generate compounds for PKC, would provide any molecules that would bind to a dehydrogenase. For example, the cofactors (common ligands) for kinases and dehydogneases, ATP and NAD/NADP, respectively, have different structures (see Exhibit 1). In addition, these enzymes use completely different chemical functionalities on the respective cofactors, the terminal phosphate of ATP and the nicotinamide ring of NAD/NADP (see Exhibit 1, highlights), and would thus have completely different positions proximal to a specificity site that would allow a linker to be placed so that the common ligand and a second ligand are oriented to bind their respective binding sites.

With regard to Rossman et al., this reference indicates that there is a structural domain (lobe) that "most probably" has essentially the same structure between phospoglycerate kinase and LDH (page 96) but in no way teaches that dehydrogenases and kinases have structural similarity, as asserted in the Office Action. Moreover, these enzymes have completely different reaction mechanisms. Dehydrogenases are oxidoreductases, whereas kinases are phosphotransferases (see Exhibit 1). The description in Rossman et al., when combined with He et al. and/or Traxler et al., would provide no motivation to modify the description in He

et al. and no reasonable expectation of success for identifying a population of bi-ligands to dehydrogenases.

The Radzicka et al. reference appears to show different inhibitors for different enzymes but no teaching of the desire to use a common ligand module to generate a population of bi-ligands that can bind to multiple members of the same enzyme family. Therefore, Radzicka et al., when combined with He et al. and/or Traxler et al. and/or Rossman et al., would provide no motivation to modify the description in He et al. and no reasonable expectation of success for identifying a population of bi-ligands to dehydrogenases. Accordingly, Applicant respectfully submits that the new claims are unobvious over He et al., alone or in combination with Traxler et al., Rossman et al., and/or Radzicka et al.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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